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8-27-97

Date

*Alexandra M. Parsons*  
Alexandra M. Parsons

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Lynn E. Spittler et al.

Serial No.: 08/288,057

Filing Date: 10 August 1994

For: PROSTATIC CANCER VACCINE

Examiner: P. Gambel

Group Art Unit: 1816

**DECLARATION OF LYNN E. SPITTLER, M.D.  
PURSUANT TO 37 C.F.R. § 1.132**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

I, Lynn E. Spittler, declare as follows:

1. I am a coinventor of the subject matter in the above-referenced application. I have been a practicing immunologist for many years. A copy of my *curriculum vitae* is attached hereto as Exhibit A.
2. I have been managing clinical trials of OncoVax<sup>TM</sup> prostate cancer vaccine which is recombinant human prostate specific antigen (rhPSA) formulated in liposomes with lipid A as adjuvant. Lipid A is a preferred adjuvant because of its ability to stimulate cell-mediated immunity in general and production of cytotoxic T cells (CTL) in particular, as opposed to alum which enhances the antibody response.
3. We conducted four clinical Phase I/II trials with 4 or 5 patients in each trial. In the first two trials, eligible patients had surgically incurable and hormone-resistant prostate cancer as

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well as intact immune responses as measured by ability to respond to recall antigens. Patients were given 1 ml of the vaccine containing 100  $\mu$ g rhPSS and 200  $\mu$ g Lipid A. In the first trial, the vaccine was administered intramuscularly in two divided doses on two extremities with intact regional lymph nodes every 30 days times 3. In this trial, one patient showed skin test sensitivity to PSA with a diameter of erythema of 18 mm, and a diameter of induration of 10 mm (when diameters of more than 5 mm are considered positive responses).

4. In the second trial, the same dosage and regimen was used except that an intravenous route was employed. Again, one of five patients showed reactivity to a skin test with PSA with a diameter of erythema of 10 mm.

5. In a third trial, the adjuvant GM-CSF was added to the protocol and the vaccine was administered with the same protocol intramuscularly. In this test, all 5 patients showed skin test reactivity to PSA with a mean diameter of erythema of 37 mm. One patient had an erythema diameter of 70x50 mm.

6. In the fourth trial, patients were treated with cyclophosphamide to diminish suppressor cell activity and the vaccine was administered intracutaneously with the addition of *Bacillus Calmette-Guerin* (BCG) at the site of vaccine administration. In this trial, 4 of the 5 patients showed a skin response to PSA with a mean diameter of erythema of 17 mm and a mean induration diameter of 9 mm.

7. The data are shown in detail on attached Exhibit B. These results show that administration of OncoVax<sup>TM</sup> is successful in eliciting a cellular response in these patients, especially in the presence of a suitable adjuvant.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Executed at Tiburon, California on 26 August 1997, by

Lynn E. Spitzer  
Lynn E. Spitzer, M.D.

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Serial No. 08/288,057  
Docket No. 204372008320

dc-89047

\*\* TOTAL PAGE.08 \*\*

## CURRICULUM VITAE

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### Education:

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|--|-----------|
| University of Michigan, Ann Arbor, Michigan                                      | 1956-1959 |
| University of Michigan Medical School<br>Ann Arbor, Michigan<br>M.D. (cum laude) | 1959-1963 |

### Training:

|                    |   |           |
|--------------------|---|-----------|
| Intern             | Highland Alameda County Hospital<br>Oakland, California   | 1963-1964 |
| Resident           | University of California<br>School of Medicine<br>San Francisco, California                             | 1964-1966 |
| Research Fellow    | H.S. Lawrence, M.D.<br>Department of Medicine - Immunology<br>New York University<br>New York, New York | 1966-1967 |
| Immunology Trainee | H. Hugh Fudenberg, M.D.<br>University of California<br>School of Medicine<br>San Francisco, California  | 1967-1969 |

Teaching Appointments and Employment:

Instructor of Medicine in Residence  
University of California  
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1970-1971

Assistant Professor of Medicine in Residence  
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1971-present

Research Associate  
Cancer Research Institute  
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School of Medicine  
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1971-1978

Director, Melanoma Center  
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1978-1990

Director of Research  
Children's Hospital of San Francisco  
San Francisco, California 94118

1978-1981

Member, Graduate Group in Comparative Pathology  
Department of Comparative Pathology  
University of California, Davis  
Davis, California

1976-1981

Senior Vice President  
XOMA Corporation  
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1981-1988

Associate Scientific Director  
Biotherapeutics, Inc.  
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1988-1989

Director 1990-present  
Northern California Melanoma Centers  
1895 Mountain View Drive  
Tiburon, California 94920

President 1991-present  
Jenner Technologies  
1895 Mountain View Drive  
Tiburon, California 94920

Awards and Honors:

Recipient: Dernham Senior Fellowship 1969-1971  
California Div. of the American Cancer Society

Recipient: Research Career Development Award 1971-1976  
National Institutes of Health

Alpha Omega Alpha (Junior year) 1961

Outstanding Young Women of America 1968

Who's Who of American Women 1972

Who's Who in the West 1973

Board Certification:

American Board of Internal Medicine 1972  
American Board of Allergy and Immunology 1974

Licensure:

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| Michigan   | 25985   |
| New York   | 96454   |
| California | C-26446 |

Memberships in Professional Societies:

American Association of Immunologists  
American Association for the Advancement of Science  
Alpha Epsilon Iota  
Western Society for Clinical Research  
American Federation of Clinical Research  
Society of Biological Therapy  
American Association for Cancer Research

Patents:

Patent #4,489,810 for "Composition and Method for Transplantation Therapy"  
Patent #4,590,071 for "Human Melanoma Specific Immunotoxins"

**PUBLIC SERVICE**

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| Allergy and Immunology Research Committee, NIAID, NIH                          | 1976-1980 |
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Editorial Boards:

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| The Journal of Immunology  | 1975-1978    |
| The International Journal of Immunopharmacology                          | 1979-1984    |
| Immunologia Clinica e Sperimentale                                       | 1982-1986    |
| Antibody Immunoconjugates and Radiopharmaceuticals<br>(Associate Editor) | 1987-present |
| Molecular Biotherapy   | 1987-present |
| Cancer Biotherapy  | 1991-present |

Manuscript Reviews:

American Review of Respiratory Disease  
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Journal of Immunology  
Journal of Infectious Diseases  
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New England Journal of Medicine  
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The Western Journal of Medicine

Special Consultant:

National Institutes of Health Grant Reviews  
National Institutes of Health Site Visits  
United States Tuberculosis Panel Task Group  
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Public Education Panel, National Multiple Sclerosis Society  
Review of Grant Applications for the National Science Foundation  
Enterprise for High School Students, Medical Apprenticeship Program,  
San Francisco, California  
Board of Directors, San Francisco Unit, American Cancer Society  
Research and Human Experimentation Committee, Children's Hospital  
of San Francisco  
U.S. Energy Research Development Administration Site Visits

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3. Cochrum K.D., Spitler L.E., Najarian J.S., and Fudenberg H.H.: A new source of large numbers of lymphocytes and studies on their culture. In Proceedings of the Third Annual Leukocyte Culture Conference. Edited by W.O. Rieke, Appleton-Century-Crofts, New York, New York, 1969, pp. 169-175.
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7. Spitler L.E., and Fudenberg H.H.: Products of interaction of antigen-sensitive leukocytes and antigen: further characterization of the mitogenic factor. J. Immunol. 104:544-549, 1970.
8. Levin A.S., Spitler L.E., States D.P., and Fudenberg H.H.: Wiskott- Aldrich syndrome: a genetically determined cellular immunological deficiency. Clinical and laboratory responses to therapy with transfer factor. Proc. Natl. Acad. Sci. 67:821-827, 1970.
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10. Spitzer L.E., Levin A.S., Huber H., and Fudenberg H.H.: Prediction of results of transfer factor therapy in the Wiskott-Aldrich syndrome by monocyte IgG receptors. In Proceedings of the Sixth Leukocyte Culture Conference. Edited by M.R. Schwartz. Academic Press, Inc., New York and London, 1972, pp. 795-803.
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12. Senyk G., Nitecki D.E., Spitzer L.E., and Goodman J.W.: The immune response to glucagon in conjugated form. Immunochemistry 9:79-110, 1972.
13. Henderson W.R., Fukuyama K., Epstein W.L., and Spitzer L.E.: Demonstration of cellular immunity to tumor-specific antigens of malignant melanoma in hamsters by inhibition of macrophage migration. J. Invest. Dermatol. 58:299-332, 1972.
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23. Astor S.H., Spitzer L.E., Frick O.L., and Fudenberg H.H.: Human leukocyte migration inhibition in agarose using four antigens: correlation with skin reactivity. J. Immunol. 110:1174-1179, 1973.
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58. Wybran J., Spitzer L.E., Lieberman R., and Fudenberg H.H.: "Active" T-cell rosettes and total T-rosettes in patients with melanoma following intratumoral inoculation of BCG: a clue to the mechanism of action of bacillus Calmette-Guerin? Cancer Immunol. Immunother. 1:153-156, 1976.

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## Gamma Interferon production after peptide stimulation of lymphocytes

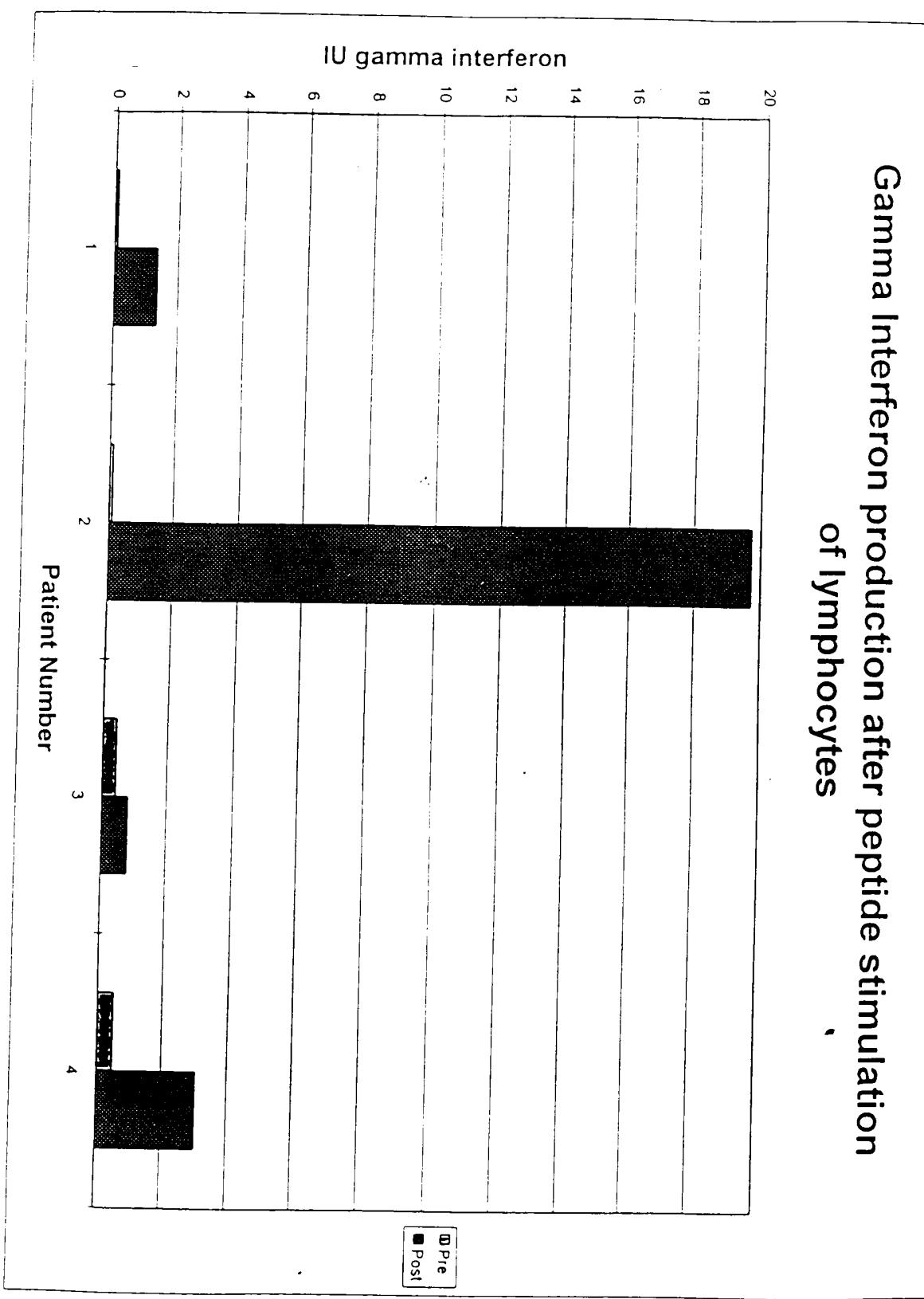


Exhibit B

## IL-4 production after peptide stimulation of lymphocytes

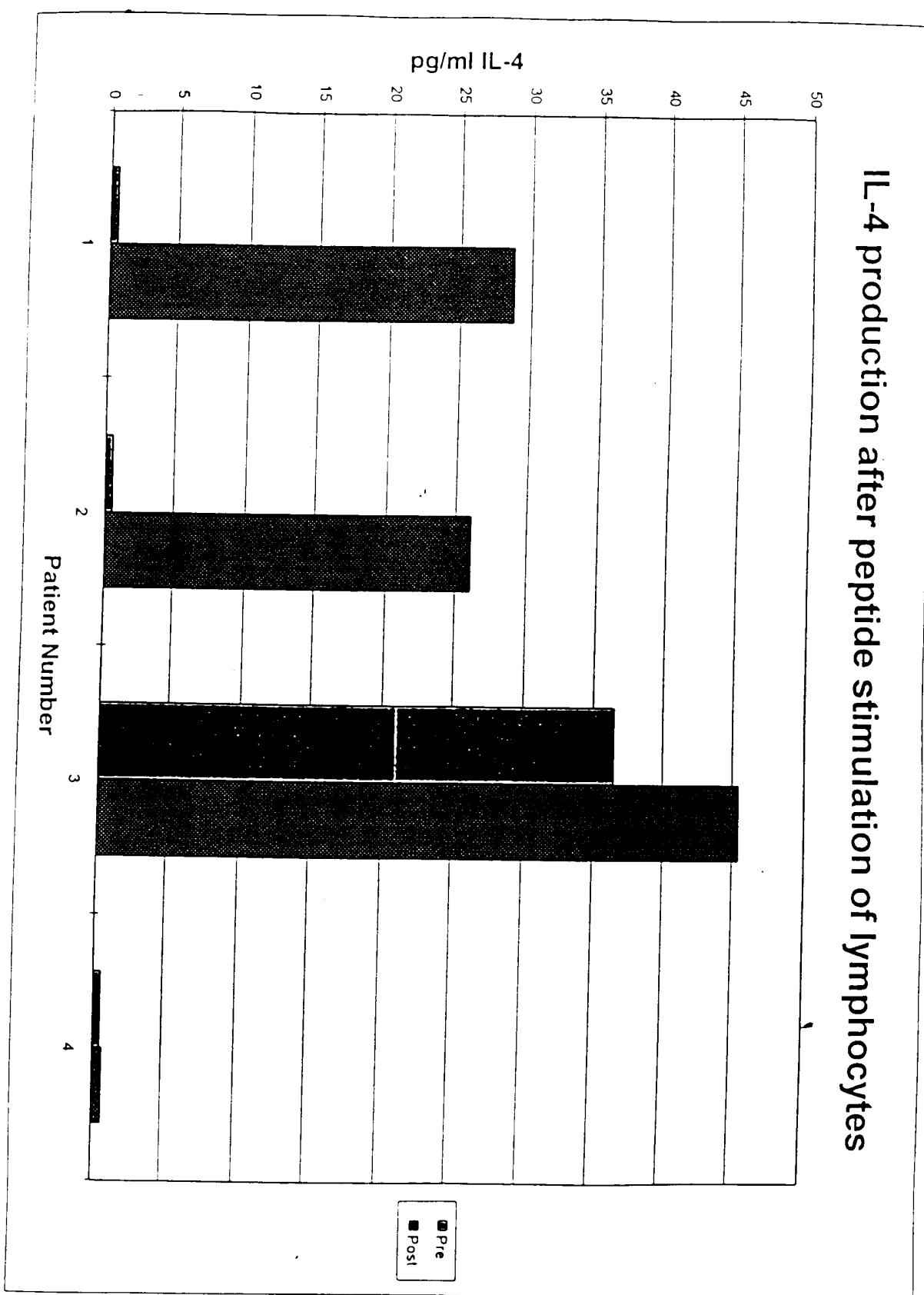


Exhibit B

**Prostate Cancer Vaccine Trials**  
**Day 90 Skin Test Results**

**Clinical Trial #1 – Immunization of Patients with Prostate Cancer with OncoVax-P™ (Prostate Cancer Vaccine)**

|         | PSA      | Buffer     |          | CEA        |          |            |
|---------|----------|------------|----------|------------|----------|------------|
|         | Erythema | Induration | Erythema | Induration | Erythema | Induration |
| 001 AW  | 2x2      | 0          | 0        | 0          |          |            |
| 002 JH  | ND       | ND         | ND       | ND         |          |            |
| 003 MD  | 18x18    | 10x10      |          |            |          |            |
| 004 MED | 0        | 0          | 0        | 0          |          |            |
| 005 HN  | 0        | 0          | 0        | 0          |          |            |
| 006 JLB | 0        | 0          | 0        | 0          |          |            |

**Clinical Trial #2 – Intravenous Immunization of Patients with Prostate Cancer with OncoVax-P™ (Prostate Cancer Vaccine)**

|        | PSA      | Buffer     |          | CEA        |          |            |
|--------|----------|------------|----------|------------|----------|------------|
|        | Erythema | Induration | Erythema | Induration | Erythema | Induration |
| 101 RT | 0        | 0          | 0        | 0          |          |            |
| 102 ER | 0        | 0          | 0        | 0          |          |            |
| 103 MC | 0        | 0          | 0        | 0          |          |            |
| 104 TM | 0        | 0          | 0        | 0          |          |            |
| 105 AF | ND       | ND         | ND       | ND         |          |            |
| 106 WC | 10X10    | 0          | 0        | 0          |          |            |

**Clinical Trial #3 – Immunization of Patients with Prostate Cancer with OncoVax-P™ (Prostate Cancer Vaccine) with GM-CSF**

|         | PSA      | Buffer     |          | CEA        |          |            |
|---------|----------|------------|----------|------------|----------|------------|
|         | Erythema | Induration | Erythema | Induration | Erythema | Induration |
| 201 AM  | 30x20    | 0          |          |            | 0        | 0          |
| 202 ASP | 35x30    | 30x30      |          |            | 7x7      | 7x7        |
| 203 CN  | 70x50    | 0          |          |            | 0        | 0          |
| 204 JA  | ND       | ND         |          |            | ND       | ND         |
| 205 GS  | 37x22    | 0          |          |            | 0        | 0          |

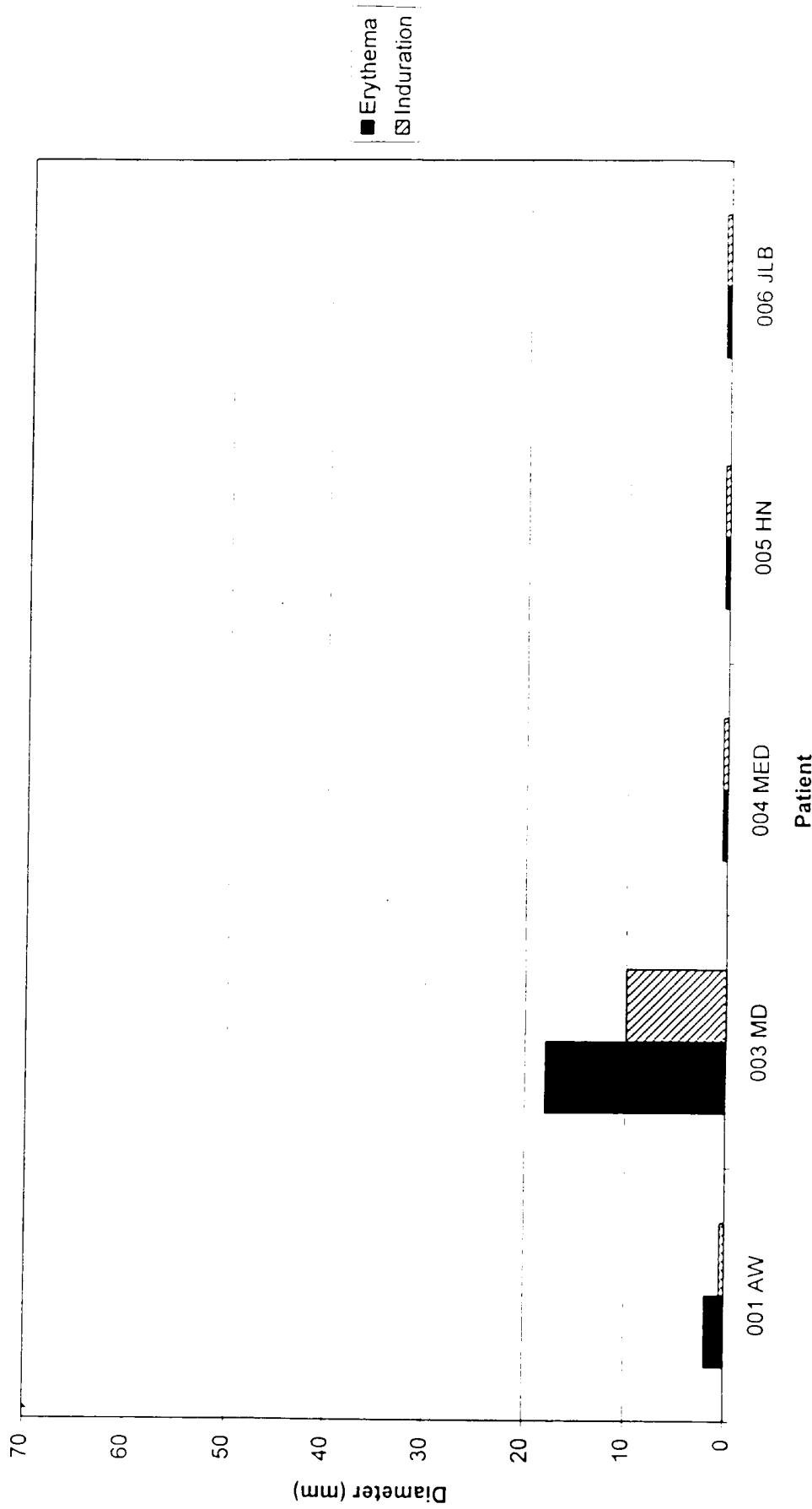
**Clinical Trial #4 – Immunization of Patients with Prostate Cancer with OncoVax-P™ (Prostate Cancer Vaccine with BCG)**

|        | PSA      | Buffer     |          | CEA        |          |            |
|--------|----------|------------|----------|------------|----------|------------|
|        | Erythema | Induration | Erythema | Induration | Erythema | Induration |
| 301 GS | 32x28    | 32x28      |          |            | 0        | 0          |
| 302 AR | 15x15    | 15x15      |          |            | 0        | 0          |
| 303 JE | 15x12    | 0          |          |            | 0        | 0          |
| 304 ML | 0        | 0          |          |            | 0        | 0          |
| 305 RD | 30x30    | 0          |          |            | 0        | 0          |

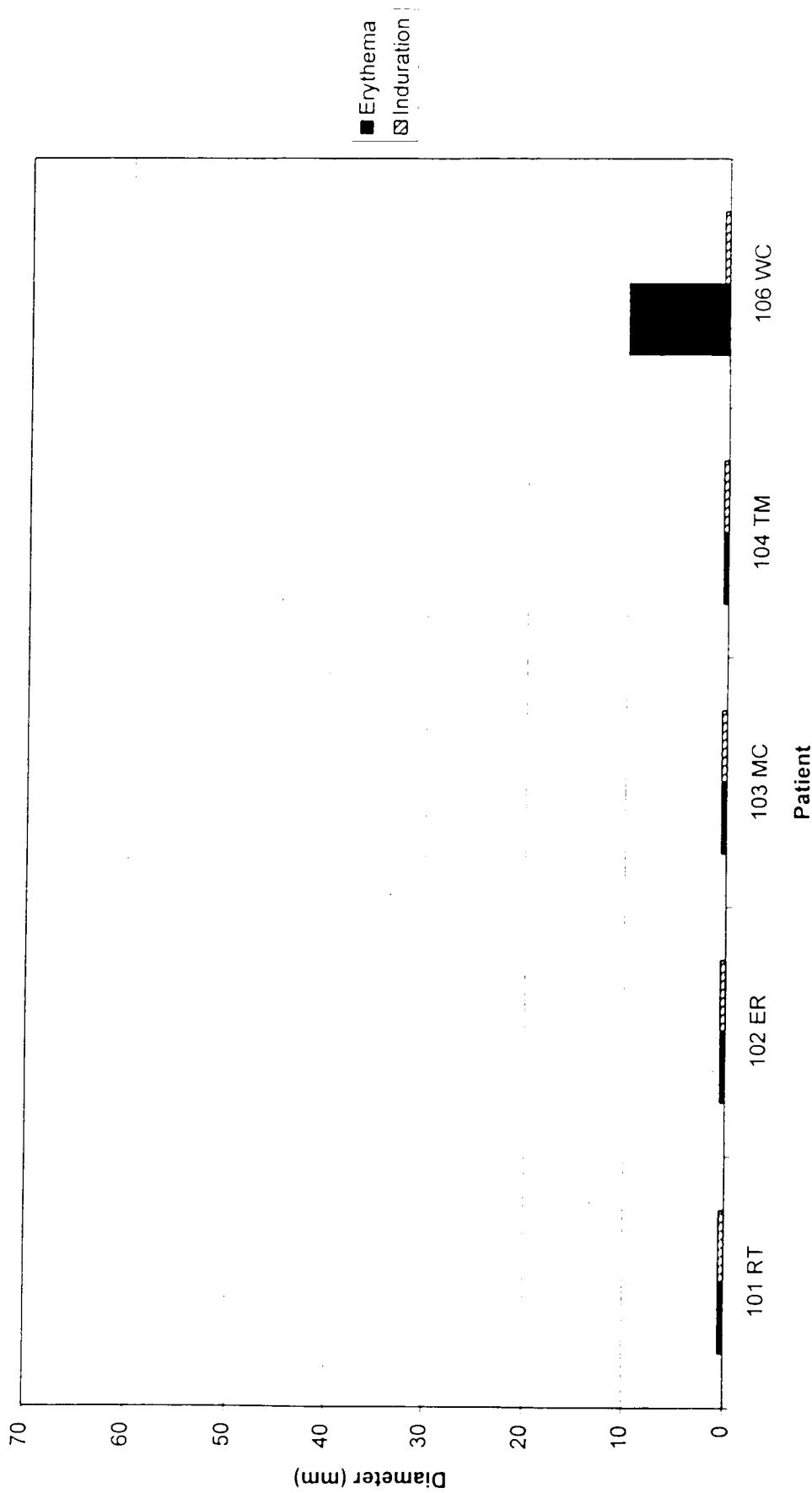
ND = Not Done

*Exh. b. + B*  
*Sprtler*

**Skin Test Reactivity to PSA**  
**Clinical Trial #1**  
**Immunization of Patients with Prostate Cancer with OncoVax-P™**

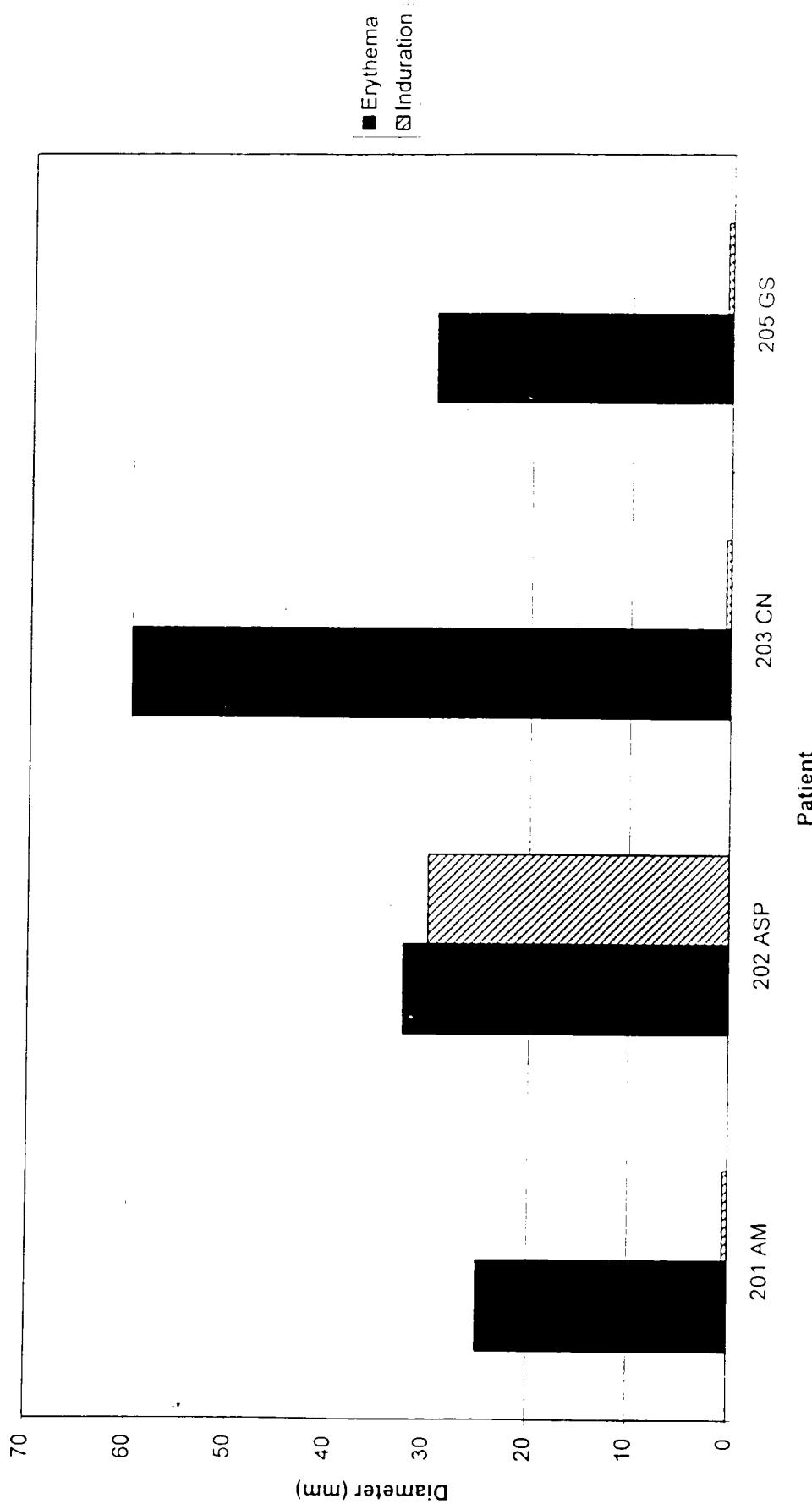


**Skin Test Reactivity to PSA**  
**Clinical Trial #2**  
**Intravenous Immunization of Patients with Prostate Cancer with OncoVax-P™**



**Skin Test Reactivity to PSA**  
**Clinical Trial #3**

**Immunization of Patients with Prostate Cancer with OncoVax-P™ with GM-CSF**



**Skin Test Reactivity to PSA  
Clinical Trial #4**

**Intravenous Immunization of Patients with Prostate Cancer with OncoVax-P™ with BCG**

